The rising incidence of Rheumatic Fever in Maori & Pacific Children: Can it be Stopped?

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• Debbie Williamson, ESR
• Julian Crane, Philippa Howden-Chapman, Sarah Jeffries, Jane Zhang, James Stanley, University of Otago
• Arlo Upton, Labtests, Auckland
• Ministry of Health for data and funding support for RF Surveillance Research
• Health Research Council (HRC) partnership programme for supporting RF Risk Factors Study & BLIS Trial (HRC, Heart Foundation, Cure Kids, Te Puni Kokiri, Ministry of Health)
Outline

• Key features of RF
• RF epidemiology
• Opportunities to intervene in causal pathway
  • Improving determinants
  • Improving specific risk/protective factors
  • Probiotic (BLIS) to reduce GAS pharyngitis
  • Screening & treating GAS pharyngitis
  • GAS vaccination
• Conclusion
Streptococcus pyogenes = Group A Streptococcus (GAS)

~20% are asymptomatic carriers
Gram positive cocci completely sensitive to penicillin

Rheumatic heart disease
Strep throat
Scarlet fever
Impetigo
Rheumatic fever
Streptococcal toxic shock
Cellulitis and necrotizing fasciitis
Key features of RF

Diseases following GAS:
• Superficial infection
  • Pharyngitis
  • Impetigo, Pyoderma
• Invasive diseases
  • Septicaemia
  • Pneumonia, osteomyelitis...
  • Necrotising fasciitis
• Toxin mediated diseases
  • Scarlet fever
  • Streptococcal toxic shock syndrome
• Post-streptococcal autoimmune sequelae
  • Acute rheumatic fever / rheumatic heart disease
  • Post-streptococcal glomerulonephritis
Key features of RF

• RF is a complex 3-stage disease:
  • GAS infection - throat (pharyngitis) and possibly skin (impetigo), may be asymptomatic
  • Acute rheumatic fever (ARF) – immune-mediated, may be asymptomatic
  • Rheumatic Heart Disease (RHD) – chronic disease, possibly requiring several ARF episodes

• RF may be difficult to diagnose
  • 2-6 weeks after a sore throat
  • Painful swelling of joint(s)
  • Fever, Tiredness, stomach ache (mesenteric adenitis)
  • Sometimes a rash or lumps under the skin (immune depositions)
  • Fidgety, unusual movements (chorea)
  • Evidence of heart murmurs signals RHD
Key Features of RF

• Largely confined to children aged 4 to 19 years (median age 9 years)
• In NZ, now almost exclusively a disease of Maori & Pacific children
• Additional association with deprivation
• Now virtually absent in developed countries
• NZ ~180 cases a year (4.5/100,000)
  • 43/100,000 in Maori children
  • 73/100,000 in Pacific Island children
• Australian Aboriginals ~600/100,000
• Fiji Prevalence of RHD in 5-15 age group = 840/100,000
RF Epidemiology
Increasing incidence ARF

Source: Ministry of Health, NMDS hospitalisation data.
RF Epidemiology
High mortality from RHD

RF is one of NZ’s biggest infectious disease killers (140 RHD deaths per year)

Source: Ministry of Health, NMDS mortality data
RF Epidemiology
Increasing ethnic inequalities

Rate Ratios
European/Other=Ref

1993
Maori = 6
Pacific = 12

2009
Rate Ratio
Maori = 36
Pacific = 72

**Fig. 1** Annual index cases and incidence rates for acute rheumatic fever in 1993–2009 for children 5 to 14 years of age. Māori (●); Pacific (●●●●); non-Māori/Pacific (●●●●).

**Source:** Milne, Lennon, et al. J Paed Child Health 2012; 48: 685-91
RF Epidemiology

Comparison with ethnic inequalities for total IDs, Children < 5 years, Ratio of Māori & Pacific ID rates to European/Other, 1989-2008

RF Epidemiology
Average annual RF rate for children 5-14, by NZDep & ethnicity, 2000-09

Causal pathway & Intervention Points

Determinants

- Population size & characteristics (e.g. age structure)
- Socio-economic & cultural conditions (e.g. poverty)
- Environmental conditions (e.g. climate)
- Health sector conditions (e.g. access to care)

Hazards (including risk/protective factors)

- Host factors (e.g. genetics, nutrition, immune status)
- Population behavior & vulnerability (e.g. household crowding)
- GAS Reservoirs (e.g. GAS carriers, infected people)
- Housing conditions (e.g. heating, dampness, ETS)
- GAS characteristics (e.g. emm-type)

Disease / Outcomes

- GAS exposure
- GAS pharyngitis
- RF
- RHD

Key: Causal pathway (→)
Suspected causal pathway (→)

Source: Oliver, Pierce, Baker. BMC Pub Health 2012; 379, 1112 - 19
Causal pathway & Intervention points

<table>
<thead>
<tr>
<th>Determinants</th>
<th>Hazards (including risk/protective factors)</th>
<th>Disease / Outcomes</th>
</tr>
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<tbody>
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<td>Population size &amp; characteristics e.g. age structure</td>
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<td>Health sector conditions e.g. access to care</td>
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</table>

<table>
<thead>
<tr>
<th>0° prevention</th>
<th>1° prevention and control measures</th>
<th>2° prevention</th>
<th>3° prevention</th>
</tr>
</thead>
</table>

- **Host factors** e.g. genetics, nutrition, immune status
- **Population behavior & vulnerability** e.g. household crowding
- **GAS Reservoirs** e.g. GAS carriers, infected people
- **GAS exposure**
- **GAS characteristics** e.g. emm-type
- **Housing conditions** e.g. heating, dampness, ETS

Key: Causal pathway

Source: Oliver, Pierce, Baker. BMC Pub Health 2012; 379, 1112 - 19
Causal pathway & Intervention points

**Altering ARF Determinants**
1. Poverty reduction
2. Improved healthcare, health literacy, housing

**Primary prevention of ARF**
3. Reduced household crowding (structural, functional)
4. Improved indoor housing env. (warm, dry, no ETS)
5. Improved nutrition
6. GAS vaccination
7. Probiotics to reduce GAS carriage/pharyngitis
8. Screening & treating household contacts of cases
9. Screening & treating GAS pharyngitis

**Secondary prevention of ARF**
10. Antibiotic prophylaxis of ARF cases
11. Echocardiography screening to detect RHD
RF Prevention Programme (RFPP)

- Government target to reduce the incidence of RF by two thirds, to 1.4 cases per 100,000 by 2017
- >$65 million of extra Budget funding
- Sore throat management through free school and community clinics – school based programme now covering ~50,000 children
- DHBs contracted for healthy housing referral service
- Awareness raising for high risk communities.
## Intervention research

<table>
<thead>
<tr>
<th>Potential intervention</th>
<th>Research</th>
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<tbody>
<tr>
<td>Improving determinants (income, education, healthcare, housing)</td>
<td>‘National’ case-control study of RF risk factors</td>
</tr>
<tr>
<td>Improving specific risk/protective factors (functional crowding, micronutrients)</td>
<td>‘National’ case-control study of RF risk factors</td>
</tr>
<tr>
<td>Probiotic (BLIS) to reduce GAS carriage/pharyngitis</td>
<td>Randomised controlled trial (RCT) of BLIS</td>
</tr>
<tr>
<td>Screening &amp; treating GAS pharyngitis (school-based, primary care)</td>
<td>Analysis of throat swabbing laboratory data &amp; linked ARF case data</td>
</tr>
<tr>
<td>GAS vaccination</td>
<td>Vaccine candidate selection &amp; ultimately clinical trial</td>
</tr>
</tbody>
</table>
RF risk factors research

Risk factors for RF:

- Age +++
- Ethnicity ++
- Poverty +
- Access to health services +
- Household crowding +/
- Household dampness +/
- Urbanisation ?
- Poor nutrition ?

Sources:
- NZ Guidelines Group, RapidE: Rheumatic Fever, 2011
**RF risk factors research**

Best quality studies show no significant association between household crowding and risk RF or RHD

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Country Time period</th>
<th>Study design</th>
<th>Outcome measure</th>
<th>Exposure measure: crowding</th>
<th>Comparison group</th>
<th>Subjects</th>
<th>No. subject</th>
<th>OR / RR, 95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurahara 2006</td>
<td>US 1998-2001</td>
<td>Case-control</td>
<td>RF</td>
<td>No. in subjects bedroom</td>
<td>Hospital controls with non-RF heart conditions</td>
<td>&lt;18yo</td>
<td>26</td>
<td>Mean cases: 1.4; controls: 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Vlajinac, 1991</td>
<td>Yugo-slavia 1982</td>
<td>Case-control</td>
<td>RF</td>
<td>&gt;2 persons / room</td>
<td>Neighbourhood &amp; school controls</td>
<td>&lt;18yo</td>
<td>148</td>
<td>OR=1.60, CI 0.61-3.00</td>
<td>NS</td>
</tr>
<tr>
<td>Oli, 1999</td>
<td>Ethiopia 1995</td>
<td>Cross-section</td>
<td>RHD prevalence</td>
<td>Persons / bedroom (2+ in univariate analysis)</td>
<td>Children without RHD</td>
<td>10-15yo</td>
<td>9378</td>
<td>OR=1.01, CI 0.99-1.02</td>
<td>NS</td>
</tr>
<tr>
<td>Coggon, 1993</td>
<td>UK 1936-1989</td>
<td>Cohort (retro)</td>
<td>Mortality from RHD</td>
<td>Crowding index 1.00+ vs. &lt;0.50</td>
<td>No RHD as adults</td>
<td>All ages</td>
<td>8138</td>
<td>-</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Source:** Baker, McDonald et al. 2012. Household crowding & risk of IDs: A systematic literature review & meta-analysis of observational studies.
RF risk factors research

Classical studies in US Air Force Base barracks in 1950s.

Acquisition of streptococcal infections increased when beds moved closer together

⇒ Biological basis for effect of crowding on ARF incidence

RF risk factors research

Cases of Rheumatic Fever (2007-2012) by percent households crowded (Canadian National Occupancy Standard)

RF risk factors research

Average annual RF first admission rates by household crowding, deprivation, income quintiles, 1996-2005

RF risk factors research

Multivariate analysis

- Risk of ARF hospitalisation in relation to CAU features
- Zero inflated negative binomial regression
- Restricted to Māori & Pacific 5-14 years, 1996-2005

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Incidence rate ratio</th>
<th>95% conf. interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household crowding</td>
<td>1.022</td>
<td>1.010-1.034</td>
<td>0.000</td>
</tr>
<tr>
<td>Household income</td>
<td>1.006</td>
<td>0.998-1.024</td>
<td>0.523</td>
</tr>
<tr>
<td>Prop. 5-14 year olds</td>
<td>1.038</td>
<td>1.005-1.071</td>
<td>0.022</td>
</tr>
</tbody>
</table>

RF risk factors research
National case-control study aims

1. Identify potentially modifiable environmental risk factors for RF, (e.g. household crowding).
2. Identify potentially modifiable host factors for RF, such as vitamin D deficiency and anaemia.
3. Establish whether current or recent skin infection is associated with an increased risk of RF.
4. Establish whether access to healthcare, including pharyngitis treatment, is protective for RF.
5. Establish whether poor oral health is associated with an increased risk of RF.
6. Establish whether specific group A streptococcus (GAS) organisms are associated with RF.
7. Contribute to identifying immunological factors associated with an increased risk of RF.
8. Establish whether certain genetic factors (the HLA-DRB1 locus) are associated with RF.
RF risk factors research
National case-control study methods

- **Design:** Case-control study
- **Location:** ‘National’ (Northern half of North Island includes ~80% ARF cases)
- **Time period:** 2 years, from 1 Sept 2014
- **Cases** = 200 ARF cases meeting NZ case definition (confirmed, probable)
- **Controls** = 2 groups
  - Matched controls – 400 (tightly matched by age group, ethnicity, NZDep, DHB, month)
  - NZ Health Survey controls – 12,000 from 3 years of NZHSs

Investigators: Michael Baker, Diana Lennon, Jason Gurney, Teuila Percival, Tony Merriman, Nevil Pierse, Debbie Williamson, Nikki Moreland, Colleen Murray, Nigel Wilson, Richard Edwards, Catherine Jackson, Jane Oliver
RF risk factors research
National case-control study methods

Data gathering:

- **Interview** with questionnaire.
- **Blood testing** for DNA, immune function markers, vitamin D, ferritin (iron stores).
- **Throat & nasal swabs** for GAS, Staph.
- **Hair sample** for nicotine.
- **Linked records**: NHI (previous hospitalisations), Dental records, School size & density, School-based throat-swabbing programme.
Probiotics

- Preventing GAS pharyngitis with BLIS-producing oral probiotic
- Bacteriocin-Like Inhibitory Substances (BLIS) naturally produced by *Streptococcus salivarius* commensal of the human tongue
- John Tagg observed that children colonised with BLIS-producing *S. salivarius* less likely to acquire *S. pyogenes*
Probiotics

Small trial of BLIS K12

- 65 children 3 - 12 years with history of recurrent strep infection
- Treated daily for 90 days with BLIS K12 (45 children) or control (20), then 6 months non-treatment
- Treated children had 90% reduction in strep pharyngitis and 40% in otitis media during treatment.
- 65% persistence of reduction during 6-month follow-up
- Follow-up study using adult subjects reported similar findings

Probiotics

• Trial – Porirua 2000 children participating in school throat swabbing programme
• Randomised to receive BLIS or placebo
• Outcome is episodes of detected GAS pharyngitis and carriage of GAS at 12 months

Investigators: Julian Crane, Michael Baker, Debbie Williamson, Nevil Pierse, Kristin Wickens, Tosh Stanley
Pharyngitis treatment

- Microbiological culture results of throat swabs performed by Auckland’s community laboratory Children 5-14 years, 2010-13 period
- 161,901 swabs with complete data
- Analyses:
  - Distribution of swabbing: incidence rates of swabbing, GAS detection and % test positivity (GAS positive swabs/number of swabs). Multivariate analyses in relation to ethnicity
  - Linkage to ARF hospitalisations: identified proportion of ARF cases with preceding throat swab (0-63 days pre-admission)
Pharyngitis treatment

Annual incidence rates of throat swabbing in 5-14 year old children in Auckland from School and PHC sources, 2010-13

Source: Jeffries, Williamson, Baker 2014
Pharyngitis treatment

Ethnic differences in incidence rates of throat swabbing, children 5-14 years, Auckland, 2010-13

Source: Jeffries, Williamson, Baker 2014
## Pharyngitis treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>ARF incidence Auckland region (ADHB, CMDHB and WDHB) 5-14 year olds</th>
<th>Swabbed in preceding 63 days before hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Rate (/100,000)</td>
</tr>
<tr>
<td>2010</td>
<td>55</td>
<td>38.4 (30.3, 48.2)</td>
</tr>
<tr>
<td>2011</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>64</td>
<td>49.1 (39.8, 59.9)</td>
</tr>
</tbody>
</table>

*Source: Jeffries, Williamson, Baker 2014*
GAS Vaccine

- Trans-Tasman (NZ-Aust) initiative announced in Feb 2013 by Key & Gillard
- Initial ~$3m from both governments as part of $30m commitment
- 3 candidate vaccines
  - Combination vaccine (Novartis) - Ready for clinical trials
  - 30-valent M-protein vaccine (Jim Dale) - Currently in Phase I clinical trials
  - J8 peptide from M-protein C-domain (Mike Good) - Currently in Phase I clinical trials

- Stated objective:
  - Phase 1 trial of candidates that achieve “acceptable coverage of local strains”
  - Progression of the strongest candidate to Phase IIB
GAS Vaccine

Many resource and technical issues

- Efficacy
- Safety
- Decision on age group
- End points
- Location of trials
- Funding
- Timing

GAS Vaccine

- **Superficial infection**
  - Pharyngitis
  - Pyoderma

- **Invasive diseases**
  - Septicaemia
  - Pneumonia, osteomyelitis...
  - Necrotising fasciitis

- **Toxin mediated diseases**
  - Scarlet fever
  - Streptococcal toxic shock syndrome

- **Post-streptococcal autoimmune sequelae**
  - Acute rheumatic fever / rheumatic heart disease
  - Post-streptococcal glomerulonephritis

Easy. High incidence. Protocols available

Possible in Ph III, but v large study, would prob need to have infant and elderly arm. Most likely as large scale effectiveness studies

Not directly. Infer as a result of protection against invasive disease

RHD not possible as Ph III – latent period too long
APSGN fairly localised, limited surveillance, epidemics
## Intervention Research

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Will it work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improving determinants (income, education, healthcare, housing)</td>
<td>Overwhelming historical evidence in favour, many co-benefits <strong>But</strong> – Takes time, huge resources, political will</td>
</tr>
<tr>
<td>Improving specific risk/protective factors (functional crowding, micronutrients)</td>
<td>Good theoretical evidence to reduce household crowding <strong>But</strong> – Poor understanding of pathophysiology of RF, Lack of empirical evidence Risk factors study will provide some data</td>
</tr>
<tr>
<td>Probiotic (BLIS) to reduce GAS carriage/pharyngitis</td>
<td>Good theoretical &amp; some empirical evidence <strong>But</strong> – Need to wait for results of trial</td>
</tr>
<tr>
<td>Screening &amp; treating GAS pharyngitis (school-based, primary care)</td>
<td>Can prevent some cases Unknown ‘herd’ effect &amp; positive co-benefits <strong>But</strong> – Limited by coverage &amp; asymptomatic infection, may promote antibiotic resistance</td>
</tr>
<tr>
<td>GAS vaccination</td>
<td>Probably the ultimate solution <strong>But</strong> - Vaccine selection &amp; clinical trials uncertain &amp; will take years</td>
</tr>
</tbody>
</table>
Conclusion

- Persistently high rates of RF in Maori & Pacific children not fully unexplained
- Prevention programmes limited by poor knowledge of pathophysiology of RF
- RFPP not associated with decline in RF to date
- Potential interventions within 2-10 years:
  - Probiotic BLIS to reduce GAS pharyngitis
  - Modifiable risk factors identified by national case-control study
  - Possible GAS vaccine trial in NZ/Australia
- Reducing poverty in NZ must remain a major goal for reducing RF & IDs more generally